Rhodium-Catalyzed Reaction of 2*H*-Azirines with Carbonyl-ene-yne Compounds Giving 1-Furyl-2-aza-1,3-dienes

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Abstract: A rhodium(II)-catalyzed reaction of carbonyl-ene-yne compounds, which are used as furylcarbene precursors, with 2*H*-azirines gave 1-furyl-2-aza-1,3-dienes as products. We propose that the title compounds are formed by the addition of furylcarbene–rhodium(II) complexes to 2*H*-azirines followed by opening of 2*H*-azirine rings.

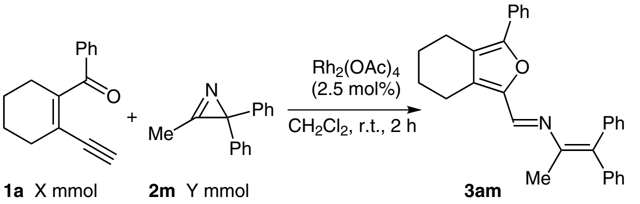
Key words: alkynes, rhodium, carbenes, azirines, ring-opening reaction

2*H*-Azirines are the smallest nitrogen-containing unsaturated heterocycles and have a C=N bond in their three-membered ring. Owing to their high strain energy (ca. 48 kcal/mol), a number of ring-opening reactions that employ strain release as a driving force have been extensively studied.[1] Whereas thermal or photochemical transformation of 2*H*-azirines is generally difficult to control, 2*H*-azirines act as vinylnitrene equivalents selectively in transition-metal-catalyzed intramolecular cyclization, leading to nitrogen-containing heterocyclic compounds.[2–6]

We have developed a variety of carbene-transfer reactions involving carbene complexes generated by the activation of alkynes with transition metals.[7,8] This type of carbene complex readily reacts with heteroaromatic compounds such as furans and thiophenes to yield addition/ring-opening reaction products efficiently.[8c,9] During our concurrent study on the nickel-catalyzed disproportional reaction of 2*H*-azirines,[10] we found a rhodium-catalyzed reaction of carbonyl-ene-yne compounds with 2*H*-azirines giving 1-furyl-2-aza-1,3-dienes.[11]

First, we employed $Rh_2(OAc)_4$ as a catalyst precursor according to the previously reported carbene-transfer reactions using carbonyl-ene-yne compounds. The reaction of carbonyl-ene-yne **1a** with azirine **2m** proceeded well, and the corresponding azadiene **3am** was obtained in 45% yield (Table 1, entry 1). Although rhodium trifluoroacetate and rhodium triphenylacetate are known to be more active in some catalytic carbene-transfer reactions, they were not effective (entries 2 and 3). The yield of **3am** was improved to 73% by using an excess of azirine **2m**, which may have suppressed the fast decomposition of carbonyl-ene-yne **1a**. The use of a rhodium(I) precursor or other transition-metal precursors led to lower yield of the product **3am**.

Table 1 Rhodium-Catalyzed Cyclopropanation of Alkenes via a Thienylcarbene Complex[a]



Entry	X (mmol)	Y (mmol)	Catalyst	Yield (%)[b]
1	0.10	0.15	$Rh_2(OAc)_4$	45
2	0.10	0.15	$Rh_2(OCOCF_3)_4$	20
3	0.10	0.15	$Rh_2(OCOCPh_3)_4$	2
4	0.20	0.10	$Rh_2(OAc)_4$	33
5	0.10	0.30	$Rh_2(OAc)_4$	62
6	0.10	0.50	$Rh_2(OAc)_4$	73
7	0.10	0.50	$[RhCl(cod)]_2$	36
8	0.10	0.50	$[RuCl_2(CO)_3]_2$	43
9	0.10	0.50	$[PtCl_2(C_2H_4)]_2$	47

[a] Reaction conditions: **1a** (X mmol), **2m** (Y mmol), and $Rh_2(OAc)_4$ (2.5 μmol), CH_2Cl_2 (1.5 mL).
[b] The yields were determined by ^1H NMR analysis using nitromethane as internal standard.

Table 2 summarizes the scope of the reaction with respect to 2*H*-azirines.[12] Another 2,2,3-trisubstituted azirine **2n** also reacted under the optimized conditions to give azadiene **3an**[13] in 80% isolated yield. The reaction of 2,3-diaryl-substituted 2*H*-azirines gave the corresponding azadienes as single stereoisomers in high yields (71–86%, entries 3–6). In the case of 2-methyl-3-phenyl-2*H*-azirine, however, the ring-opening reaction product **3as** was obtained in only 37% yield, which could be due to the faster formation of a dimer of **1a** [(*E*)-1,2-difurylethylene; entry 7].

The scope of carbonyl-ene-yne compounds **1** is summarized in Table 3. Aromatic substituents such as 4-methoxy, 4-chloro, and 2-methyl groups on the phenyl ketone moiety were also available, and the yields of azadienes were

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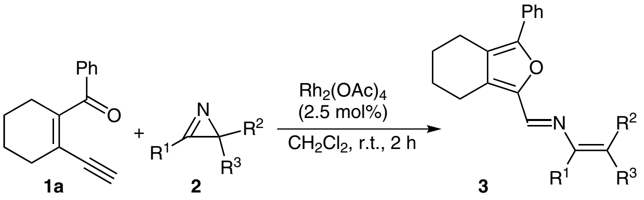
in the range of 57–80%. In addition to cyclohexane-fused carbonyl-ene-yne compounds, aliphatic substrate **1e** also reacted to give azadiene **3en** with a simple furan ring. The reaction of **2n** with thiocarbamoyl-ene-yne compound **1f**, which is also used as a highly reactive carbene precursor,[8c] afforded the corresponding thiophene-substituted product, albeit in low yield (20%).

Table 2 Rhodium-Catalyzed Reaction of Carbonyl-ene-yne **1a** with 2*H*-Azirines **2**[a]



1a + **2** → **3**

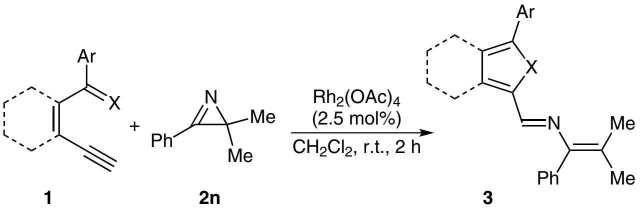
Entry	2	R^1	R^2	R^3	3	Yield (%)[b]
1	**2m**	Me	Ph	Ph	**3am**	73
2	**2n**	Ph	Me	Me	**3an**	94 (80[c])
3	**2o**	Ph	Ph	H	**3ao**	84
4	**2p**	4-$MeOC_6H_4$	Ph	H	**3ap**	86
5	**2q**	4-ClC_6H_4	Ph	H	**3aq**	81
6	**2r**	Ph	4-ClC_6H_4	H	**3ar**	71
7	**2s**	Ph	Me	H	**3as**	37

[a] Reaction conditions: carbonyl-ene-yne **1a** (0.10 mmol), azirine **2** (0.50 mmol), $Rh_2(OAc)_4$ (2.5 mol%), 1,2-dichloroethane (1 mL).
[b] Determined by ^1H NMR analysis using nitromethane as internal standard.
[c] Isolated yield.

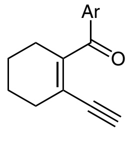
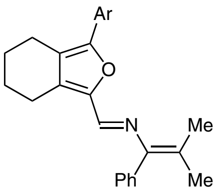
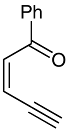
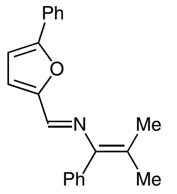
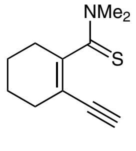
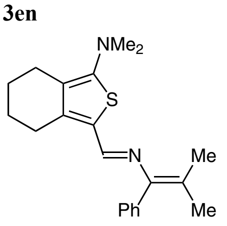
On the basis of previously reported metal-catalyzed carbene addition reactions with 2*H*-azirines,[7] a proposed catalytic cycle for the reaction of **1a** and **2n** is depicted in Scheme 1. According to the proposed cycle, the furylcarbene–rhodium complex **B** would be generated by nucleophilic attack of the carbonyl oxygen on the coordinated alkyne in complex **A**. Next, the nitrogen atom on the azirine would add to the carbene to give rhodium-containing azirinium ylide **C**,[14] which would undergo opening of the three-membered ring of the azirine moiety to afford azadiene **3an** with the regeneration of the dirhodium catalyst.[15]

Finally, we attempted the derivatization of the produced 2-azadienes. Although the Diels–Alder reactions using 2-azadienes as diene units are well-known transformation methods,[16] to the best of our knowledge, hydride reduction of 2-azadienes to imines or amines has not been reported. The two-step reduction of azadiene **3an** with $LiAlH_4$ in Et_2O at 40 °C followed by hydrolysis gave secondary amine **5** in good yield (70% for the two steps; Scheme 2). The formation of imine **4** was observed by ^1H NMR analysis after the first reduction.[17]

Table 3 Rhodium-Catalyzed Reaction of Carbonyl-ene-yne Compounds **1** with 2*H*-Azirine **2n**[a]

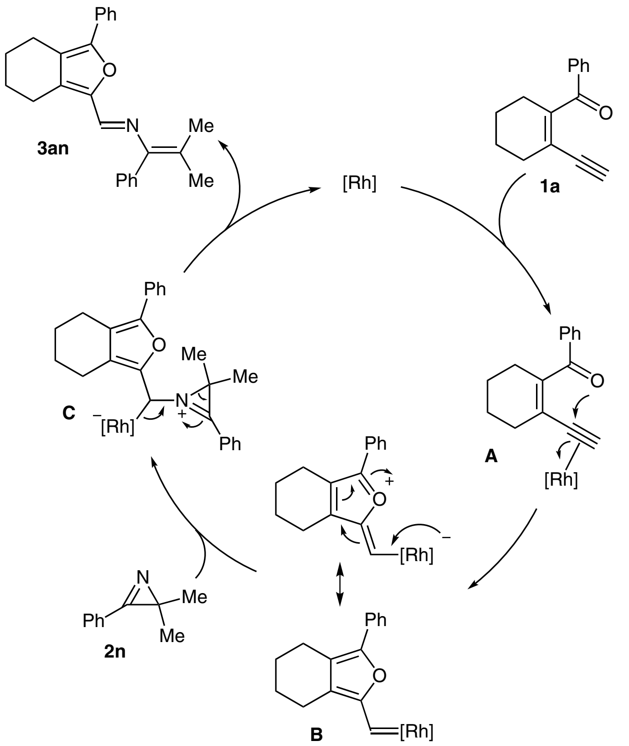


1 + **2n** → **3**

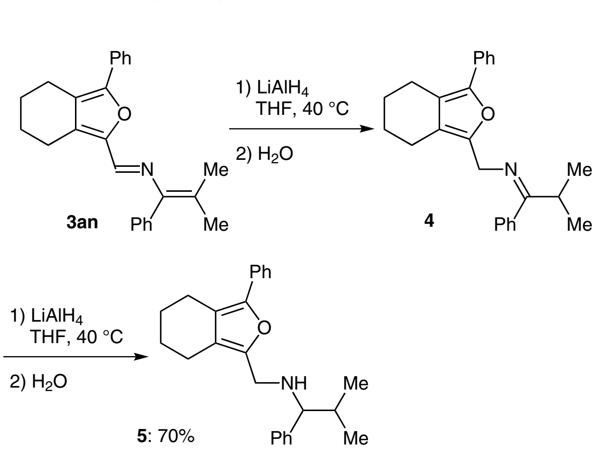
Entry	Carbonyl-ene-yne 1	Azadiene 3	Yield (%)[b]
			
1	**1a** (Ar = Ph)	**3an**	80
2	**1b** (Ar = 4-$MeOC_6H_4$)	**3bn**	65
3	**1c** (Ar = 4-ClC_6H_4)	**3cn**	80
4	**1d** (Ar = 2-MeC_6H_4)	**3dn**	57
5	 **1e**	 **3en**	49
6	 **1f**	 **3fn**	20[c]

[a] Reaction conditions: carbonyl-ene-yne **1** (0.10 mmol), azirine **2n** (0.50 mmol), $Rh_2(OAc)_4$ (2.5 mol%), 1,2-dichloroethane (1 mL).
[b] Isolated yield.
[c] Determined by ^1H NMR analysis using nitromethane as internal standard.

In conclusion, we have developed a rhodium-catalyzed carbene-addition/ring-opening reaction of 2*H*-azirines by using carbonyl-ene-yne-compounds as carbenoid precursors. The resulting 1-furyl-2-aza-1,3-dienes are readily reduced to aliphatic amines with a furan moiety. Further investigations of such ring-opening reactions of other heterocyclic compounds are underway.



Scheme 1 A proposed catalytic cycle for the rhodium-catalyzed reaction of carbonyl-ene-yne **1a** with azirine **2n**



Scheme 2 Transformation of azadiene **3an** into amine **5**

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(12) **General procedure for the catalytic reactions:** A solution of [$Rh_2(OAc)_4$] (1.1 mg, 2.5 μmol), carbonyl-ene-yne **1** (21.0 mg, 0.10 mmol), and azirine **2** (0.50 mmol) in CH_2Cl_2 (1.0 mL) was stirred at r.t. for 2 h. The reaction mixture was filtered through a pad of Florisil with EtOAc, and the solvent was removed under reduced pressure. The yield of azadiene **3** was estimated by ^{1}H NMR analysis of the crude product with nitromethane (0.10 mmol, 5.4 μL) as internal standard. The remaining azirine **2** was distilled off by Kugelrohr distillation. The residue was passed through a pad of Florisil to give azadiene **3**.
Azadiene 3an: Yield: 28.3 mg (0.080 mmol, 80%); pale-orange oil. ^{1}H NMR ($CDCl_3$): δ = 1.67 (s, 3 H), 1.71–1.82 (m, 4 H), 2.25 (s, 3 H), 2.74–2.90 (m, 4 H), 7.11 (d, *J* = 6.8 Hz, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 7.34 (t, *J* = 6.8 Hz, 1 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.42 (t,

J = 7.3 Hz, 2 H), 7.55 (s, 1 H), 7.65 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (CDCl$_3$): δ = 19.4, 21.8, 22.4, 22.5, 22.9, 23.1, 121.3, 124.7, 126.8, 127.1, 128.1, 128.4, 128.5, 130.2, 131.1, 132.8, 137.0, 144.3, 144.8, 146.5, 148.3. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{25}$H$_{26}$NO: 356.2014; found: 356.2014.

Azadiene 3bn: Yield: 24.9 mg (0.065 mmol, 65%); pale-yellow oil. ^{1}H NMR (CDCl$_3$): δ = 1.66 (s, 3 H), 1.68–1.85 (m, 4 H), 2.25 (s, 3 H), 2.65–2.89 (m, 4 H), 3.82 (s, 3 H), 6.90 (d, J = 8.8 Hz, 2 H), 7.11 (d, J = 7.3 Hz, 2 H), 7.34 (t, J = 7.8 Hz, 1 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.53 (s, 1 H), 7.59 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (CDCl$_3$): δ = 21.8, 22.5, 22.5, 22.8, 23.2, 55.3, 114.0, 119.7, 124.4, 126.3, 127.1, 128.4, 130.3, 132.3, 137.2, 144.2, 144.8, 145.9, 148.6, 158.7. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{26}$H$_{28}$NO$_2$: 386.2120; found: 386.2115.**Azadiene 3cn**: Yield: 31.3 mg (0.080 mmol, 80%); pale-yellow oil. ^{1}H NMR (CDCl$_3$): δ = 1.67 (s, 3 H), 1.70–1.85 (m, 4 H), 2.25 (s, 3 H), 2.70–2.90 (m, 4 H), 7.11 (d, J = 7.3 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 2 H), 7.36 (t, J = 7.3 Hz, 1 H), 7.42 (t, J = 7.3 Hz, 2 H), 7.53 (s, 1 H), 7.57 (d, J = 8.8 Hz, 2 H). ^{13}C NMR (CDCl$_3$): δ = 19.4, 21.9, 22.4, 22.5, 22.9, 23.1, 121.8, 125.9, 127.2, 128.1, 128.6, 128.7, 129.8, 130.3, 132.5, 133.3, 137.0, 144.1, 144.8, 146.7, 147.3. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{25}$H$_{25}$ClNO: 390.1625; found: 390.1637.

Azadiene 3dn: Yield: 21.0 mg (0.057 mmol, 57%); pale-orange oil. ^{1}H NMR (CDCl$_3$): δ = 1.66 (s, 3 H), 1.67–1.82 (m, 4 H), 2.23 (s, 3 H), 2.36 (s, 3 H), 2.54 (t, J = 5.9 Hz, 2 H), 2.88 (t, J = 6.3 Hz, 2 H), 7.09 (d, J = 7.8 Hz, 2 H), 7.15–7.22 (m, 3 H), 7.27–7.33 (m, 2 H), 7.39 (t, J = 7.3 Hz, 2 H), 7.53 (s, 1 H). ^{13}C NMR (CDCl$_3$): δ = 19.4, 20.8, 21.8, 22.2, 22.4, 22.8, 23.2, 122.0, 125.3, 127.0, 127.1, 128.0, 128.5, 129.0, 130.27, 130.31, 130.9, 132.6, 137.0, 137.1, 144.4, 144.8, 146.9, 149.9. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{26}$H$_{28}$NO: 370.2171; found: 370.2183.

Azadiene 3en: Yield: 14.8 mg (0.049 mmol, 49%); pale-orange oil. ^{1}H NMR (CDCl$_3$): δ = 1.68 (s, 3 H), 2.31 (s, 3 H), 6.72 (d, J = 3.4 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 7.12 (d, J = 6.8 Hz, 2 H), 7.28 (t, J = 7.8 Hz, 1 H), 7.33–7.38 (m, 1 H), 7.39 (d, J = 6.3 Hz, 2 H), 7.42 (d, J = 7.3 Hz, 2 H), 7.45 (s, 1 H), 7.73 (d, J = 6.8 Hz, 2 H). ^{13}C NMR (CDCl$_3$): δ = 19.3, 22.0, 107.4, 115.4, 124.3, 127.3, 128.0, 128.6, 128.7, 130.1, 130.3, 134.4, 137.0, 143.2, 144.2, 152.9, 155.7. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{21}$H$_{20}$NO: 302.1545; found: 302.1536.

(13) Geometry of azadiene **3ar** was determined by ^{1}H NMR NOE experiments, see Figure 1.

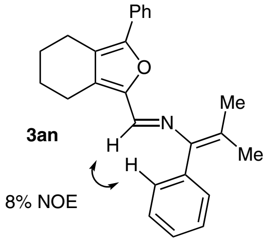

Figure 1 Geometry of azadiene **3ar**

(14) Fragmentation from metal-free azirinium ylide or a metallacycle generated by the insertion of **B** into the C–N single bond of **2n** could be an alternative route to the 2-azadiene.

(15) The reason for stereoselective formation of **3ao**–**3ar** may be that the transition state from **C** settles into the conformation with the least steric hindrance.

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(17) **Reduction of azadiene 3an:** To a solution of azadiene **3an** (35.5 mg, 0.10 mmol) in THF (1.0 mL) was added LiAlH$_4$ (19.0 mg, 0.50 mmol) in one portion, and the reaction mixture was stirred at 40 °C for 2 h. The reaction was quenched with 1.0 M aq NaOH, and extracted with EtOAc. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated under vacuum to give a crude product imine **4**. The residue was used in the next reduction without further purification. The second reduction of imine **4** was performed under the same conditions as the first reduction of azadiene **3an**. The crude mixture was subjected to column chromatography on silica gel (hexane–EtOAc, 10:1) to give amine **5**.

Imine 4: ^{1}H NMR (CDCl$_3$): δ = 1.11 (s, 3 H), 1.14 (s, 3 H), 1.60–1.80 (m, 4 H), 2.43 (t, J = 5.5 Hz, 2 H), 2.75 (t, J = 5.9 Hz, 2 H), 2.85 (septet, J = 7.0 Hz, 1 H), 4.31 (s, 2 H), 7.12–7.40 (m, 6 H), 7.42 (t, J = 7.0 Hz, 2 H), 7.58 (d, J = 7.0 Hz, 2 H).

Amine 5: Yield: 25.0 mg (0.070 mmol, 70%); pale-yellow oil. ^{1}H NMR (CDCl$_3$): δ = 0.73 (d, J = 6.4 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H), 1.60–1.79 (m, 4 H), 1.83 (br s, 1 H), 1.85 (octet, J = 6.8 Hz, 1 H), 2.17–2.35 (m, 2 H), 2.75 (t, J = 6.4 Hz, 2 H), 3.33 (d, J = 7.3 Hz, 1 H), 3.45 (d, J = 14.6 Hz, 1 H), 3.63 (d, J = 14.2 Hz, 1 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.23–7.35 (m, 5 H), 7.37 (t, J = 7.8 Hz, 2 H), 7.60 (d, J = 7.3 Hz, 2 H). ^{13}C NMR (CDCl$_3$): δ = 19.4, 19.6, 20.4, 22.8, 23.0, 23.4, 34.4, 42.4, 68.3, 118.9, 120.3, 124.1, 125.9, 126.8, 127.9, 128.3, 128.5, 132.2, 142.4, 145.4, 146.8. HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for C$_{25}$H$_{30}$NO: 360.2327; found: 360.2324.